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Abstracts

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Immunohistologic patterns in lupus nephritis: Correlations with clinical data and prognosis. *S. Bertoli, A. Bucci, M. T. Porri, G. Mazzucco, P. Stratta, P. Scalia, E. Mariani, C. Robaudo, and G. Busnach. Divisione di Nefologia e Dialisi degli Ospedali Ca' Granda, Policlinico e S. Carlo Borromeo, Milano, Cattedra di Nefrologia dell'Università, Genova, and Cattedra di Nefrologia e Istituto di Anatomia Patologica dell'Università, Torino, Italy.* The immunohistologic aspects in lupus nephritis have been correlated with a few clinical parameters, but the relationship with the presenting syndromes or the long-term clinical course has not been fully investigated. We evaluated 122 renal biopsies in 112 patients affected by lupus nephritis with light microscopy and immunofluorescence (IF). On the basis of IF, we classified them into four groups: *(1)* mesangial deposits (8 cases); *(2)* mesangial and focal subendothelial (15 cases); *(3)* diffuse subendothelial (73 cases); *(4)* subepithelial (22 cases). Four cases were negative. Deposits of IgG, Clq, and C3 were present in over 75% of the cases; IgM, between 62% and 85%; IgA and C4, between 12% and 65% of the cases, in correlation with the severity of the disease. A strict correspondence between IF groups and light microscopy classes (numbered according to Appel et al) was not found. By contrast, a good correlation between the presence and quantity of subendothelial deposit and histologic or clinical activity was observed. Groups 2 and 3 were characterized by different clinical syndromes: acute nephritic syndrome was present only in group 3, whereas nephrotic syndrome or isolated urinary abnormalities were observed in groups 2, 3, and 4. The progression of renal failure was largely more frequent in the diffuse subendothelial group and rare or absent in the other groups. Death from extrarenal causes was more frequent, but not exclusive, in that group. Within this group, a higher percent of deposits and a higher intensity were correlated with a worse prognosis.

Hyperaldosteronism, renin-aldosterone dissociation, and increased sensitivity to angiotensin II in chronic renal failure. *G. Bruschi, P. Coruzzi, A. Recusani, C. Ravanetti, L. Musiari, A. Novarini, and A. Borghetti. Istituto di Semeiotica Medica dell'Università, Parma, Italy.* There is no agreement on the state of aldosterone regulation in chronic renal failure (CRF), for reported alterations have varied from hyperaldosteronism to hypoaldosteronism. We found plasma aldosterone concentration (PAC) measured by radioimmunoassay to be elevated in 32 patients with CRF (male, 20; female, 12; ages, 61 ± 10 yr) in comparison with controls (males, 12; female, 1; ages, 52 ± 15 yr). PAC was 27.7 ± 35.8 ng/dl in CRF and 5.4 ± 4.2 in normals. Sodium intake was 50 to 60 mEq/day in all the subjects, and all of them were in supine position. In most of the patients, hyperaldosteronism was associated with normal or low-normal plasma renin activity, although some had very high values (CRF, 0.7 ± 1.7 ng/ml/hr; controls, 0.4 ± 0.25 ng/ml/hr). The renin-aldosterone (R-A) dissociation of uremic patients resulted in a shifted R-A correlation line in comparison with normal subjects. In CRF, the metabolic efficiency of circulating aldosterone might be doubted, because of the loss of functioning renal mass. However, sodium repletion and potassium depletion were found in 12 patients whose exchangeable sodium and potassium were measured (exch. Na in CRF, 45.1 ± 7.5 mEq/kg, in controls, 41.2 ± 2.9; exch. potassium in CRF, 33.7 ± 7.1 mEq/kg, in controls, 45.3 ± 3.3). The stimulation of adrenal glands by graded subpressor doses of angiotensin (0.1, 0.2, 0.5, 1, and 2 ng/kg/min for periods of 30 min each) led to a more marked increase of PAC in CRF patients than in control subjects (mean PAC in CRF, 7.0 ± 3.7 ng/dl; in controls, 2.5 ± 2.9 ng/dl). The possibility of artifacts must be considered. Assay of plasma extracted with dichloromethane led to lower PAC values, thus suggesting that water-soluble metabolites crossreact with the antibody used; however, it failed to lower PAC more in uremic than in normal subjects; the former still had higher values of PAC after plasma extraction. Thus, our data suggest that, in CRF, PAC is inappropriate to ECF volume and renin activity, possibly being at least in part responsible for the potassium depletion and hypertension that are frequently observed in this disease. The higher PAC in CRF may be due either to impaired aldosterone metabolism by renal tissue, or to increased adrenal production, possibly by known or unknown factors in the uremic environment.

Platelet-activating factor, a mediator of platelet aggregation: Effect of corticosteroids. *G. Camussi, F. Bussolino, C. Tetta, M. C. Deregibus, G. Segoloni, R. Ragni, and A. Vercellone. Laboratorio di Immunopatologia e Cattedra di Nefrologia dell'Università, Torino, Italy.* Platelet-activating factor (PAF), recently identified as 1-0-alkyl-2-acetyl-sn-glyceryl-3-phosphorylcholine, has been shown to be a mediator of inflammation, which causes in vitro and in vivo platelet activation. PAF release has been obtained from different cellular types: polymorphonuclear neutrophils, monocytes, macrophages, basophils, and platelets themselves. One × 10^{-11} M of PAF determines rabbit and human platelet aggregation and "release reaction" independently from ADP- and arachidonic acid- (AA) mediated pathways. PAF-dependent platelet activation requires Ca^{++} and Mg^{++}, metabolic energy, the activation of serine esterase, and a membrane phospholipase A_2. Prostacyclin, which increases intracellular cAMP levels, inhibits platelet aggregation induced by PAF. We have studied the effect of membrane-active drugs and corticosteroids on platelet aggregation induced by PAF. Xilocaine (10^{-3} M), mepacrine (10^{-4} M), which are membrane active drugs, and reserpine (5×10^{-5} M), imipramine (5×10^{-4} M), which protect red blood cells from hypotonic lysis, were strong inhibitors of PAF-induced platelet aggregation similarly to 6-methyl prednisolone (6-MP) (5×10^{-3} M) and hydrocortisone (5×10^{-3} M). These corticosteroids prevented the PAF-platelet interaction in a dose-dependent mode and were uneffective on ADP- or AA-mediated pathways. Dexamethasone (5×10^{-2} M), which shows greater antiinflammatory potency than 6-MP, inhibited (50%) the action of PAF only at high doses. Intravenous injection of PAF (0.8 μg/kg) in rabbits induced dramatic and reversible thrombocytopenia, similar to that occurring during IgE-induced systemic anaphylaxis or after injection of immune-complex (IC). Previous administration of 20 mg/kg of 6-MP prevented PAF induced thrombocytopenia. Our studies demonstrate that corticosteroids are inhibitors of PAF activity in vitro and in vivo and provide a plausible rationale for the empiric use of high doses of corticosteroids in patients with thrombocytopenia occurring in anaphylactic shock and in the acute phase of systemic lupus erythematosus.

Immune-induced leukopenia: A role for the aggregation of polymorphonuclear neutrophils in systemic lupus erythematosus. *G. Camussi, G. Segoloni, C. Tetta, F. Bussolino, P. Stratta, R. Ragni, and A. Vercellone. Laboratorio di Immunopatologia e Cattedra di Nefrologia dell'Università, Torino, and Divisione d Nefrologia e Dialisi, Ospedale S.G. Battista, Torino, Italy.* The pathogenesis of leukopenia such as that occurring during SLE, a human model of immune complex (IC) disease, has been related to the intravascular aggregation of polymorphonuclear neutrophils (PMN) with attendant leukostasis and leukoembolization in the capillary network as a mechanism of tissue injury. Beside C5a anaphylatoxin, in vitro IC-induced PMN aggregation is also brought

about by cationic proteins (CP) released from IC-stimulated PMN through their surface receptors for the Fc fragment of complexed immunoglobulin and the C3b complement fraction. However, in vivo both C5a and CP are rapidly cleaved to low molecular weight, desarginated products, C5a des Arg, and CP des Arg, that, although devoid of anaphylatoxin activity, exhibit a striking potentiation of their native molecules' aggregating activity on PMN. Recently, we showed that PMN aggregation induced by C5a, CP, C5a des Arg, and CP des Arg is mediated by a final common effector substance, a low molecular weight phospholipid with a biologic activity, physicochemical characteristics, and behavior on thin layer chromatography identical to antigen-stimulated, IgE-sensitized rabbit basophil-derived platelet-activating factor (PAF), initially described as a mediator of anaphylaxis capable of inducing platelet aggregation and release of their granular content. PAF itself is a potent inducer of PMN aggregation, which, as for platelets, is independent from the other known pathways of aggregation, that is, the ADP and arachidonic acid/thromboxane A_2-mediated pathways of aggregation. In vivo studies in rabbits injected with IC, C5a, and CP have shown that the acute neutropenia is related to the intravascular aggregation of PMN leading to their massive accumulation in the pulmonary capillary network, a series of phenomena that have been temporally and quantitatively correlated with the recovery of PAF in the plasma. In systemic lupus erythematosus (SLE), leukopenia is commonly assumed as an index of disease activity. We studied 10 SLE patients in the clinically active phase of the disease and found leukopenia (WBC, 4000/mm^3) in 40%. The possibility that the mechanisms implicated in vitro and in vivo in the rabbit may be operating in man has been indirectly suggested by the following observations: the in vivo interaction between IC and PMN surface receptors as detected with our immunohistologic technique; the in vivo release of CP; the depletion of releasable PAF from PMN and their in vitro unresponsiveness to the aggregating stimuli such as C5a, CP, C5a des Arg, CP des Arg and PAF; the in vivo extraction of PAF from plasma during the neutropenia associated with the active phases of SLE. However, some considerations are in order. Although the IC-PMN interaction well correlated with the clinically evident activity of the disease, the same did not hold true for the neutropenia. The lack of correlation may be explained in view of the fact that soluble factors rather than IC have a major bearing on the pathogenesis of neutropenia. The in vitro unresponsiveness of PMN to the aggregating stimuli may reflect an in vitro masking of surface receptors or a state of metabolic overstimulation.

Neurosympathetic response to hemodialysis in patients with or without dialysis-induced hypotension. *G. Cannella, G. B. Picotti, M. D. Galva, G. Gregorini, R. Maiorca. Divisione di Nefrologia Spedali Civili, Brescia; Istituto di Farmacologia, Facoltà di Medicina dell'Università di Milano, Italy.* Six normotensive (N) and six dialysis-hypotension prone (H) uremic patients were studied. They were submitted, during an interdialysis day, to a postural test (5 min upright) and on the following day to a regular dialysis (D) lasting 3 hr. Blood samples for radioenzymatic assay of plasma norepinephrine (NE) were drawn before and after standing and before, during (every 40 min), and after dialysis. *Results.* Resting NE in H group was significantly higher than in N group either before standing or before dialysis. After 5 min upright, NE rose in both N and H group and to a similar extent than in 12 healthy subjects taken as control. During D, plasma NE rose continuously in both groups, significantly after about 80 min, in a similar way than in 6 controls, volume-depleted by furosemide injection (1 mg/kg of body wt, i.v.). Body weight, plasma proteins, hematocrite behaved in a similar way, during hemodialysis, in both uremic groups, whereas a significant decrease in blood pressure was observed earlier in the H group. *Conclusions.* Dialysis hypotension does not seem to depend on a neurosympathetic deficiency but appears to be related to a hypotensive effect borne by dialysis itself. Such a hypotensive stimulous might be prevailing in some patients rather than in others, leading perhaps to a chronic neurosympathetic stimulation with higher than normal plasma NE levels.

Prognosis of acute rejection requiring dialysis. *A. Cantaluppi, A. De Vecchi, A. Tarantino, G. Banfi, G. Montagnino, and C. Ponticelli. Divisione di Nefrologia e Dialisi, Ospedale Policlinico, Milano, Italy.* In 224 renal transplant recipients, 114 early rejection episodes have been diagnosed within 1 month after transplantation; 32 out of them complicated by renal insufficiency requiring dialytic treatment within 4 days since onset has been defined "acute anuric rejection episodes." These episodes appeared within the 2nd and the 29th day after transplantation, and were characterized by increasing proteinuria (62% of cases), fever (56%), thrombocytopenia (31%), arterial hypertension (28%), and reduced natriuresis (25%). The incidence of this last sign only was significantly different (lower) as compared to natriuresis observed in early nonanuric acute rejections. Renal bioptic findings in 13 cases were: "slight" rejection (1), "moderate" rejection (6), "severe" rejection (4), and "irreversible" rejection (2). In 24 cases (75%), a partial (16%) or total (59%) recovery of renal function allowed withdrawal of dialytic treatment, while 8 patients had their allograft removed. Prognosis was not correlated with any clinical or biochemical data or with anuria's length. On the contrary, bioptic findings have useful prognostic indications, 7 out of 7 patients with a "slight" or "moderate" rejection had a recovery of renal function while only in 1 out of 6 patients with "severe" or "irreversible" rejection renal failure reversed. As a whole, either short-term or long-term prognosis of "acute anuric rejection episodes" did not significantly differ from that of acute early rejection episodes. In conclusion, our data underline that oligoanuria during an early acute rejection episode does not constitute a negative prognostic sign, being not necessarily an expression of rejection severity.

Glomerular dynamics in pregnant rats: A micropuncture study. *A. Dal Canton, G. Conte, C. Esposito, G. Fuiano, R. Guasco, D. Russo, M. Sabbatini, F. Uccello, and V. E. Andreucci. Cattedra di Nefrologia Medica, Seconda Facoltà di Medicina, Università, Napoli, Italy.* Although a marked rise in GFR in pregnancy has been repeatedly noticed in the past 30 years, the mechanisms responsible for this phenomenon have not yet been clarified. In the present study glomerular dynamics were investigated by micropuncture in pregnant Wistar-Munich rats. Nonpregnant rats were used as controls. Glomerular capillary pressure (P_G), intratubular pressure (P_T), and pressure in the 1st-order peritubular capillaries were measured with a servo-nulling device. Single nephron filtration rate (SNGFR) was measured as the clearance of chemical inulin in single nephrons. Single nephron filtration fraction (SNFF) was calculated from arterial and peritubular blood protein concentration. Afferent arteriole blood flow, that is, glomerular blood flow (GBF), resistance of single afferent (R_a) and efferent arteriole (R_e), effective filtration pressure at the afferent end (EFP_a), and at the efferent end (EFP_e) of the glomerulus, and the ultrafiltration coefficient (K_f) were calculated. In pregnant rats SNGFR increased from 27.7 to 43.2 nl/min/g of kidney wt as a mean. R_a was markedly reduced, accounting for a rise both in GBF (from 155.3 to 257.6 nl/min/g of kidney wt) and in P_G (from 45.3 to 53.4 mm Hg). Because P_T was unchanged, EFP_a rose proportionally to P_G; also EFP_e was increased from a control value not different from zero to 13.2 mm Hg. This filtration pressure disequilibrium allowed calculation of a definite value of K_f (0.037 nl/mm Hg/sec) in pregnant rats. Minimum possible value of K_f in control rats was 0.044 nl/mm Hg/sec. Pregnancy caused no change in R_e or in SNFF. These results show that SNGFR is enhanced in pregnancy due to an increase both in effective filtration pressure and in glomerular plasma flow. The rise in SNGFR is partially opposed by a reduction in K_f.

Some aspects of circulating immune complexes in primary glomerulonephritis. *P. Dall'Aglio, G. Balestrieri, L. Allegri, C. Chizzolini, E. Ciccone, D. Pagani, and A. Tincani. Cattedra di Immunologia Clinica e Istituto di Clinica Medica e Nefrologia dell'Università, Parma e Servizio di Immunologia Clinica, Spedali Civili, Brescia, Italy.* In 103 patients with different biological types of primary glomerulonephritis (PGN), we investigated circulating immune complexes (CIC) simultaneously in minimal change GN (MCGN) (14 cases), focal glomerulosclerosis (FGS) (9 cases), membranous GN (MGN) (19 cases), membranoproliferative GN (MPGN) (23 cases), mesangioproliferative GN (MSPGN) (28 cases), 18 of these with mesangial predominant IgA deposits. We used three tests: 125 Clq binding assay (Clq-BA), conglutinin binding test (CGB-SP) and precipitation in 3.5% polyethilenglycol (PEG), each of these revealing different types of CIC. The CIC precipitated by PEG were further investigated by double radial immunodiffusion (DRID) in agarose gel, against monospecific sera anti IgG, IgA, IgM, Clq, C_1, C_3, C_4, and by ultracentrifugation (16 hr at

×87,000*g*) in linear 10 to 40% sucrose gradient, to evaluate their molecular weight, using as markers human IgG (7S), IgM (19S), and catalase (11,2S). Every test revealed CIC with different frequency: Clq-BA more often in MGN (38.9%) and in FGS (33.3%), CGB-SP in MGN (44.4%) and in MPGN (44.4%), and PEG in MCGN (71.4%). Very rarely were all three tests simultaneously positive. In different histologic types of PGN, the ultracentrifugation showed CIC of various mol wts, and frequently the contemporary presence of CIC of different mol wts. In CIC precipitated by PEG, IgM, and Clq were observed in MCGN, while IgG and complement were revealed more frequently in other PGN; IgA were rarely found, also in MSPGN with mesangial predominant IgA deposits. In conclusion, our studies showed different CIC for composition, mol wt, and biological activities in PGN, sometimes in relation to histologic lesions. In addition the comparison between CIC investigated by DRID and immune complexes (IC) revealed by immunofluorescence in renal biopsies frequently showed differences. Furthermore, this result is suggestive for IC formed in some types of PGN at the renal level.

Acid-base balance on peritoneal dialysis with acetate and lactate buffers. *G. La Greca, S. Biasioli, S. Cortesi, A. Fabris, M. Feriani, E. Pisani, C. Ronco, and F. Zen. Divisione di Nefrologia e Dialisi e Laboratorio di Analisi Chimico-Cliniche, Ospedale S. Bortolo, Vicenza, Italy.* To evaluate acid-base balance on intermittent peritoneal dialysis (IPD) and on continuous ambulatory peritoneal dialysis (CAPD), 40 studies were performed on 20 patients under conditions of IPD with acetate buffer (5 patients), IPD with lactate buffer (5 patients), CAPD with acetate buffer (5 patients), and CAPD with lactate buffer (5 patients). Commercial dialysis solutions containing 41.5 mM acetate and 43.7 mM lactate for IPD were utilized; 38.5 mM was the content both of acetate and lactate for CAPD. Acetate, lactate, and pyruvate concentrations in blood and dialysate were determined at different times (0, 30, 60, 120, 240, and 480 min) of intermittent dialysis; blood samples for blood gas analysis were also drawn at the same time. Blood and dialysate samples were taken at the end of each exchange (4 to 5 per day) for 6 to 7 days a week in patients on CAPD. Calculations for acetate, lactate, and bicarbonate kinetics of IPD and CAPD conformed with those of Tolchin (1977) and consequently "adapted" to PD. Thus, it was possible to quantify the balance of the buffers, their mass transfer rate, the bicarbonate generated, and the percentage of buffer converted to bicarbonate. IPD kinetics of acetate and lactate are similar, the main difference being a lower and significant percentage of lactate converted to bicarbonate (45%) in comparison to acetate one (71%). On CAPD, the kinetics of the two buffers are quite different: while the serum lactate level was found constantly low (mean 0.97 ± 0.33 mmoles/liter), the acetate showed constant high levels (5.12 ± 3.34 mmoles/liter). Thus there is a different utilization of the two buffers between the "acute intermittent" treatment (IPD) and "continuous" one (CAPD). While on IPD, there are not any important differences between the two buffers. On CAPD, lactate seems to be better and safer than acetate, for instance, serum bicarbonate values are very constant with lactate (27.7 ± 2.13 mmoles/liter) while with acetate there resulted a certain trend to exceed physiologic values (29.5 ± 1.7 mmoles/liter). When used, acetate concentration in the dialysate for CAPD must be less than 38.5 mmoles/liter.

Natural history of calcium nephrolithiasis in Italy. *F. Masi, E. Rovelli, F. Malberti, N. Colleoni, G. Colussi, L. Luciani, and M. Surian. Divisione di Nefrologia e Dialisi degli Ospedali Ca'Granda e S. Carlo Borromeo, Milano, Italy.* Little is known about the natural history of calcium nephrolithiasis in Italy. Most of the known studies on this topic have been performed in foreign populations, with different socioeconomic and dietetic habits. We have retrospectively studied 476 stone formers out of 4846 ambulatory nephropathic patients from two different nephrologic centers. Calcium stones (oxalate and/or phosphate) were present in 290 (69.7%) patients, of whom 58% were males and 42% females. Complete metabolic and clinical data were available in 200 of these patients: 41% had idiopathic hypercalciuria (IH), 7.5% hyperuricosuria (HU), 13.5% IH + HU, 5.5% primary hyperparathyroidism (HP), 3.5% sponge kidney, 9% urinary tract malformations, 1.5% renal tubular acidosis (the last three groups were not considered further); 18.5% of patients had no clinical or metabolic disturbance (NMD). IH and HU were prevalent in males (76.3%) and HP in females (64.3%). Mean age at onset was in the 3rd to 4th decade of life, and was slightly later in hyperuricosuric patients. Number of stones/patient/year was higher in patients with HP and lower in patients with NMD. Calcium nephrolithiasis had a high recurrence rate (after 10 years followup 74% of patients had at least one recurrence and 60% had 3 or more stones formed); 40% of recurring patients had their first recurrence within one year from the first stone and most of these patients had a second recurrence in the following year. Clinical history and metabolic evaluation help to select patients at high risk of recurrence, in whom treatment is indicated.

Serum ferritin in hemodialyzed patients: Correlations with other parameters of anemia. *S. Mombelloni, E. Movilli, G. Pizzocolo, M. Ravelli, M. Campanini, G. Cancarini, L. Ascari, A. Albertini, and R. Maiorca. Divisione di Nefrologia e Dialisi, II Laboratorio di Analisi chimico-cliniche e Laboratorio di Ormonologia e Tossicologia, Spedali Civili, Brescia, Italy.* We have studied 51 hemodialyzed patients (30 males, 31 females) undergoing regular dialysis therapy (RDT) from 0.7 to 14 years (mean, 5.9 years) receiving about 100 mg per month of Fe gluconate i.v. We evaluated the patients monthly for one year following: serum ferritin, transferrin, % TIBC, hematocrit (Hct), hemoglobin (Hb). Serum ferritin concentrations in RDT patients were significantly higher ($P < 0.001$) than in normal subjects, even when considered without iron therapy. The normal difference between sexes disappears. In our cases, serum ferritin shares a direct correlation with serum iron, an inverse correlation with transferrin, a direct correlation with % TIBC, and only in males, an inverse correlation with Hb and Hct. Serum ferritin levels are still high after 6 months from the withdrawal of iron therapy, and rise promptly after starting treatment. The reason serum ferritin shares an inverse correlation with Hb and Hct could be that patients with lower ferritin and higher Hct are those who are able to metabolize iron more easily; the reasons for this are obscure. The fact that this trend is shown only by males could be due to the higher levels of testosterone in this population. Serum ferritin seems to be the best guide to iron supplementation in RDT patients.

Effect of sodium intake on plasma norepinephrine, renin activity and their responses to head-up tilt in essential hypertension. *A. Morganti, T. Pickering, J. Lopez-Ovejero, and J. Laragh. Istituto di Ricerche Cardiovascolari, CNR, Milano, Italy, and The New York Hospital Cornell Medical Center, New York.* Because the state of sodium homeostasis is reported to affect plasma norepinephrine (NE), which reflects the activity of the sympathetic nervous system (SNS), and this last is known to control the renin response to various stimuli, our aim in this study was to examine *(1)* whether the changes in plasma renin activity (PRA) induced by different sodium intakes are associated with concomitant changes in NE, and *(2)* whether the state of sodium balance influences the responses of NE and PRA to a neural stimulus such as the assumption of upright posture. Thus, we measured NE and PRA in 8 patients with uncomplicated essential hypertension both in the supine position and after 30 min of 65° head-up tilt after 5 days on low (L), medium (M), and high (H) sodium intake (10, 100, and 300 mEq/day, respectively). In the supine position, NE was similar on L and M (312 ± 49 and 334 ± 35 pg/ml) while it was significantly lower on H (200 ± 32 pg/ml) ($P < 0.01$ for both L and M); in contrast PRA was always different (L, 5.7 ± 2.2; M, 2.9 ± 1.1; H, 0.9 ± 0.4 ng/ml/hr) ($P < 0.05$ at least). After 30 min of tilt, the increments in NE were similar (L, 419 ± 103; M, 268 ± 46; H, 346 ± 87 pg/ml) while those in PRA were different in absolute values (L, 4.8 ± 2.0; M, 2.4 ± 1.0; H, 0.5 ± 0.2 ng/ml/hr) ($P < 0.01$ for all) but similar when expressed in percent of supine values (L, 83 ± 13; M, 89 ± 14; H, 73 ± 21%). These data show that H decreases both basal NE and PRA whereas L increases PRA only; thus, while the responses of the SNS and of renin to sodium loading may be related, that of renin to sodium deprivation is probably mediated through nonneural mechanisms. Also, it appears that neither the responsiveness of the SNS nor that of renin to head-up tilt are influenced by the state of sodium balance.

Hemodialysis-induced leukopenia: Role of direct cell-to-membrane interaction. *A. Pacitti, G. Segoloni, G. Triolo, C. Tetta, M. Messina, F. Bussolino, G. Camussi, R. Ragni, P. F. Martini, R. Coppo, and A. Vercellone. Cattedra di Nefrologia dell'Università e Divisione di Nefrologia e Dialisi, Ospedale S.G. Battista, Torino, Italy.* Extracorporeal

circulation during hemodialysis results in a transient, profound neutropenia, which has been related to intravascular polymorphonuclear neutrophil (PMN) aggregation with ensuing leukostasis and leukoembolization, particularly in the pulmonary microvasculature. Although C5a anaphylatoxin and its carboxypeptidase B-derived desarginated product C5a des Arg are in vitro able to mediate PMN aggregation, their role in vivo remains to be defined, as during hemodialysis complement activation occurs late and in vitro is rather slow (45 min) as compared with the fugacity (5 to 30 min) of hemodialysis-induced neutropenia. Our studies could explain these discrepancies, suggesting the possibility of a direct cell-to-membrane interaction. In vitro purified human PMN, incubated with cuprophan but not with polyacronitrile membranes, release their lysosomal enzymes and cationic proteins (CP), which are capable of inducing PMN aggregation. As for C5a, CP are in vivo cleaved to CP des Arg by serum carboxypeptidase B. Recently, we demonstrated both in vitro and in vivo that C5a-, C5a des Arg-, CP and CP des Arg-induced PMN aggregation is triggered by a final, common, effector substance platelet-activating factor (PAF), a low molecular weight phospholipid, with a potent aggregating activity on platelets leading to the release of their granular content. PAF is fully active on PMN as on platelets in the presence of ADP scavengers and cyclooxygenase inhibitors, thus suggesting activation of a unique metabolic pathway independent from the other known pathways of PMN aggregation, that is, the ADP and arachidonic acid/thromboxane A_2-mediated pathways. PAF-induced PMN aggregation is completely and selectively inhibited by lipid-soluble drugs such as glucocorticoids (6-methylprednisolone). The present study concerns the in vitro effect of cuprophan membrane on purified human PMN. Our data show that PMN in the presence of cuprophan but not of polyacronitrile undergo a process of degranulation, and PAF is released in the supernatant. The interaction between dialysis membrane and cells leading to the release of neutrophil aggregant activity is related to its biologic properties. However, complement activation and release of neutrophil aggregant activity are two processes that occur independently and can therefore be studied separately.

Calcium metabolism in nephrotic syndrome of children. *F. Perfumo, R. Oleggini, R. Gusmano. Divisione di Nefrologia e Dialisi, Istituto G. Gaslini, Genova, Italy.* Patients with nephrotic syndrome (NS) have several disorders of calcium metabolism. These include hypocalcemia, hypocalciuria, and decreased intestinal absorption of calcium. Vitamin D circulates bound to a low-molecular weight protein, and urinary loss of the globulin might contribute to the development of calcium abnormalities. We studied 16 patients, 2 to 14 years of age, with normal renal function and proteinuria (100 mg/m^2/hr), at the clinical onset of NS. The parameters evaluated were: Ca, P, Mg, alk. phosphatase, PTH, calcitonin, 25-OHCC, Gc-globulin in serum and Ca, P, and OH-proline on 24-hr urine collections. The results showed: *(a)* a significant reduction of serum calcium, urinary calcium, vitamin D-binding globulin, and 25-OHCC; *(b)* a rise in serum PTH, in particular 6/16 children had PTH values above 1 ng/ml; *(c)* a direct and significant correlation between blood Gc-globulin and serum albumin and an inverse significant relation between blood Gc-globulin and the degree of proteinuria. We conclude: *(1)* abnormalities of calcium metabolism in NS appear early in the course of the disease; *(2)* therapeutic implications are important to avoid damage to a growing skeleton.

C3d assay in idiopathic and secondary glomerulonephritis. *G. Pertosa, C. Pecoraro, E. La Raia, P. Stanziale, R. Gallo, V. E. Andreucci, and F. P. Schena. Istituto di Clinica Medica II dell'Università di Bari. Cattedra di Nefrologia Medica della II Facoltà di Medicina dell'Università di Napoli, Italy.* The behavior of the complement system is routinely evaluated by measuring C3 with radial immunodiffusion. Truly, this method may indicate a normal value if its accelerated catabolism is counterbalanced by an increased synthesis. In contrast, the assay of C3d, the stable fragment of C3, could reveal the participation of the complement system even in those cases where there are normal serum levels of C3. Thus, C3d values have been investigated in 74 patients with idiopathic glomerulonephritis (GN) and in 31 cases of secondary GN. Results have shown significant high levels of C3d in different idiopathic GN with normal C3 values. The incidence of increased C3d levels varied from 35% in cases of endoextracapillary GN, to 51% in patients with membranoproliferative GN. Two different behaviors of C3d and C3 levels were found in secondary GN: *a)* high levels of C3d associated with normal C3 levels in 30 to 57% of the GN, *(b)* normal C3d values associated with reduced levels of C3. These data suggest that in idiopathic and secondary GN with normal C3 values and high levels of C3d, the activation of the complement system is probably masked by an increased synthesis of C3, whereas in secondary GN with low levels of C3 and normal values of C3d, the activation of the complement system is associated to insufficient synthesis of C3. Therefore, C3d measurement is a valid parameter for revealing the activation of the complement system and low synthesis of C3.

Rheumatoid kidney. *M. Ragaiolo, R. Boggi, A. Corvetta, E. Lombardo, A. Martino, V. Mioli, R. Montironi, and C. Parravicini. Cattedre di Patologia Medica, di Anatomia umana normale, di Anatomia Patologica e di Nefrologia dell'Università. Divisione di Nefrologia e Dialisi, Ospedale Umberto I°, Ancona, Italy.* In 35 patients affected by chronic rheumatoid arthritis (ARA's and Stenbrocker's criteria were used for the diagnosis), we have studied the "rheumatoid kidney". Excluding all the patients who previously suffered from complications (that is, urinary stones and infections) or treated by phenacetin and gold therapy, we have selected 17 patients. All were submitted to clinical, functional, and metabolic investigations, and, in 8 of them, to hystologic observations (light, immunofluorescence, and electronic) by renal biopsy. *Clinically* we have observed microscopic haematuria and slight proteinuria in 16 cases; 1 case with no pathologic urinary findings and no cases with a nephrotic or acute nephritic syndrome. *Histologically* we have observed by light microscopy some glomerular damages, that is, focal or diffuse mesangial hypercellularity in all the cases, segmental thickening of the capillary walls in 4 cases, intimal arteriolar thickening in 4 cases, and in all the cases a slight atrophy of the tubules with focal interstitial fibrosis and linphomonocyte infiltration. By the immunofluorescence observations, granular deposits of the fibrinogen in the capillary walls (3 cases), of IgM (4 cases) and of C_3 (1 case), were observed. IgG and IgA were always negative and a slight fibrinogen positivity on the tubular walls was noted in 3 cases. *Electron microscopic* picture confirmed the focal mesangial increase (cells and matrix) in all the cases, endothelial proliferation in 1 case, no dense deposits in capillary walls, splitting of the tubular walls in 4 cases, focal increase in collagen interstitial fibers in all the cases. By these observations we can conclude that the rheumatoid kidney has some slight polymorphic lesions but no pathognomonic picture. Simultaneously, a significant correlation between the clinical and hystological pattern and the positivity of the serological screening was noted.

Nephritic factor in membranoproliferative glomerulonephritis. *P. Stanziale, G. Pertosa, C. Pecoraro, E. Vox, R. Gallo, C. Grasso, F. P. Schena, and V. E. Andreucci. Cattedra di Nefrologia Medica della Facoltà di Medicina dell'Università, Napoli. Istituto di Clinica Medica II dell'Università, Bari, Italy.* Nephritic factor (NeF) has been detected in various types of glomerulonephritis, its highest incidence being in membranoproliferative glomerulonephritis (MPGN). Up to now, neither a clear pathogenic nor a meaningful prognostic role of NeF has been elucidated. In this study, NeF was looked for by immunoelectrophoretic and hemolytic methods in 24 patients with primary MPGN (18 type I, 6 type II) and in 11 patients with secondary MPGN. Immunochemical dosage of complement fractions (Clq, C_4, C_3, C_3d) and of properdin factor B was carried out. NeF was found in 5 patients (28%) with type I and in 3 patients (50%) with type II MPGN. NeF was associated with low levels of C_3 in 3 out of 5 patients with type I MPGN; in all these patients, however, C_3d was elevated. C_4, instead, was normal, while Clq fluctuated from low to normal values. C_3 was low in 6, and normal in 4 out of 10 NeF-negative patients. In all NeF-positive patients with secondary MPGN (1 with LES, 4 with primary cryoglobulinemia), low values of Clq, C_4, C_3, and properdin factor B were found. Quantitative measurements of NeF at regular intervals throughout the study showed consistent changes in the NeF concentration in many patients and a complete, although transient, disappearance of NeF in 4 patients. A significant relation between NeF and the course of renal disease was observed only in 3 patients with type II MPGN, in which the existence of NeF was associated with a progressive and rapid worsening of renal function. *Conclusions.* NeF is particularly frequent both in primary and in secondary type II MPGN. In the latter, NeF indicates a poor prognosis.

Lupus nephropathy: Involvement of coagulation in blood, tissues and urine. *P. Stratta, C. Canavese, M. Dogliani, M. Messina, M. Rotunno, and A. Vercellone. Divisione di Nefrologia e Dialisi, Ospedale S.G. Battista, Cattedra di Nefrologia dell'Università, Torino, Italy.* During systemic lupus erythematosus (SLE), the involvement of the coagulation system can be due to two possible pathogenetic mechanisms: the activation of the coagulation and fibrinolitic cascade unleashed by immunological processes and the formation of antibodies against omeostasis factors. We studied a first group of patients including 21 subjects with nephropathy due to SLE. Renal biopsies were performed and patients were classified according to Appel: 2 in class II, 2 in class III, 13 in class IV, 2 in class V, 2 in class VI. Results were compared with a second group (14 SLE patients) with systemic onset and scarse renal involvement and a third group of 70 patients with primary glomerulonephritis with different hystopathologic picture. The following parameters were studied: Quick time, PTT, TEG, fibrinogen and platelet blood level, dripping time, spontaneous and DPA-induced platelet aggregation according to Breddin, collagen, adrenalin, ristocetin, platelet adhesiveness, urinary and tissue fibrinolysis, blood and urinary FDP, schistocytes in peripheral smear, paracoagulation test, blood and urinary level of endoplatelet release products (endoplatelet factor 4 and β-1-thromboglobulin). Signs of a systemic activation of coagulation that are frequent during the acute stage of systemic Lupus (80.9%) appear only sporadically in SLE with prevailing renal involvement and never in primary glomerulonephritis. Platelet pathology (absent in primary glomerulonephritis) is commonly found in SLE (70%) and in renal lupus erythematosus (40%): reduced response to aggregating agents, reduced adhesiveness and presence of antiplatelet antibodies; the latter two are found independently of the clinical stages of the disease in systemic LE and they disappear during remission in renal lupus erythematosus. Circulating anticoagulants are rare (7%) and appear only during the acute stage of the systemic disease; they disappear during remissions. Tissue fibrinolysis evaluated with the Todd Pandolfi hystochemical method resulted constantly high in lupus nephropathies while it was normal or low in primary glomerulonephritis. Urinary fibrinolysis is normal while urinary FDP are often high also in primary glomerulonephritis. Our results do not prove a systemic or local activation of coagulation during primary glomerulonephritis: in nephropathies due to SLE, a local activation is reported but signs in blood are less marked than in systemic LE.

Effect of captopril on blood pressure, plasma renin activity and autonomic nervous system in low-normal renin essential hypertension. *A. Sturani, C. Chiarini, E. Degli Esposti, A. Gattiani, A. Masi, A. Santoro, A. Umile, A. Zuccalà, and P. Zucchelli. Divisione di Nefrologia e Dialisi, Ospedale M. Malpighi, Bologna, Italy.* Captopril was administered to 12 essential hypertensive patients with low-normal renin in order to test its effectiveness in reducing blood pressure (BP) and to determine whether the inhibition of converting enzyme (CE) could interfere with sympathetic neural activity. Captopril, at a daily dose of 150 to 450 mg, significantly reduced BP in 5 patients (responders) and had no effect in 7 patients (nonresponders). In the responders, a significant reduction in mean arterial pressure (MAP) was already observed with a daily dose of 75 mg (from 127 ± 11 to 119 ± 14 mm Hg, $P < 0.05$) and a further significant reduction was observed at the end of treatment (from 127 ± 11 to 111 ± 11 mm Hg, $P < 0.01$). In the nonresponders, no significant variation in MAP was observed (from 132 ± 10 to 128 ± 11 mm Hg). A significant fall in resting heart rate (HR) was observed both in responders and nonresponders on 75 mg daily (from 70.8 ± 4.2 to 65.4 ± 4.0 beats/min, $P < 0.01$ and from 77.0 ± 4.1 to 73.7 ± 3.8 beats/min, $P < 0.05$, respectively). This fall remained significant in the responders, while it was lost in the nonresponders at the end of treatment. The drug did not significantly change plasma renin activity in any patient. Plasma noradrenaline was significantly reduced by captopril in the responders (from 531 ± 81 to 210 ± 26 ng/liter, $P < 0.05$) and remained unchanged in the nonrespnders (from 231 ± 36 to 248 ± 45 ng/liter). The response of BP and HR to Valsalva maneuver, tilt test, mental stress test, and cold-pressure test was similar before and after treatment in all patients. On the contrary, the bradycardia induced by diving test was significantly greater after treatment than before therapy (from 21 ± 3 to 29 ± 4 beats, $P < 0.05$ in the responders, and from 32 ± 11 to 38 ± 9 beats, $P < 0.05$ in the nonresponders). In conclusion, captopril also normalizes BP in patients with low-normal renin essential hypertension. The effect of CE inhibition plasma noradrenaline and BP suggests that captopril may interfere with the release of catecholamines, and this interference may contribute to the hypotensive effect of the drug. The physiologic study suggests an overall integrity of the baroreceptor reflex arc and vascular reactivity to stress before as well as after treatment with captopril. The drug decreases resting HR and enhances the bradycardia induced by diving test, suggesting that captopril may cause overactivity of the parasympathetic system.

Vitamin D metabolites in patients with early renal failure: Effects of dietary phosphate restriction and calcium supplementation. *N. Tessitore, B. Lund, B. Lund, O. H. Sorensen, E. Bonucci, G. Maschio. Divisione di Nefrologia, Istituti Ospitalieri, Verona e I Cattedra di Anatomia Patologica dell'Università, Roma, Italy, and Department of Orthopedic Surgery, Frederiksborg Hospital, Hillerod, and Department of Medicine E and F, Copenhagen, Denmark.* In 20 patients with early renal failure (GFR, by iothalamate clearance, 23 to 63 ml/min), we have evaluated the serum values of vitamin D metabolites and bone histology before and after 8 months of a diet containing 700 mg of phosphate and 600 mg of calcium. In 10 of them, oral calcium supplementation (1,000 mg) was added. The basal values of plasma calcium and phosphate were normal, i-PTH values were only mildly increased (2.95 ± 1.27 mU/ml; normal range, 1 to 2.4), serum levels of $25(OH)D_3$ were in the low-normal range, while serum concentration of $1.25\ (OH)_2D_3$ and $24,25(OH)_2D_3$ were significantly reduced in comparison with controls (10.02 ± 8.61 pg/ml and 0.87 ± 0.84 ng/ml, respectively; normal range, 18 to 48 pg/ml for $1.25(OH)_2D_3$ and 0.6 to 2.3 ng/ml for $24,25(OH)_2D_3$). Bone biopsy showed normal histology in 45% of our patients, osteomalacia in 30%, and osteomalacia and increased resorption in 25% of them. No correlation was found between bone histology and both PTH and vitamin D metabolites levels. The only significant correlation was found between $25(OH)D_3$ and $24,25(OH)_2D_3$ values ($r = 0.56$). After the treatment, there were no significant changes in GFR, plasma calcium and phosphate, i-PTH, $25(OH)D_3$, $1,25(OH)_2D_3$ and bone histology, while $24,25(OH)_2D_3$ levels were significantly increased in those patients treated with calcium supplementation too (from 0.73 ± 0.72 to 1.66 ± 0.59 ng/ml; $P < 0.025$). Moreover, in the same patients the correlation between $25(OH)_2D_3$ and $24,25(OH)_2D_3$ was stricter ($r = 0.92$). Our data show an impaired 1-alfa-hydroxylation even in the early phases of renal failure and suggest that the normal levels of $24,25(OH)_2D_3$ could explain the mild degree of hyperparathyroidism and bone lesions found in those patients with incipient renal failure early treated with a phosphate-restricted diet and calcium and vitamin D supplements.